



UNDER SECRETARY OF DEFENSE
4000 DEFENSE PENTAGON
WASHINGTON, D.C. 20301-4000

PERSONNEL AND
READINESS

JUL 19 2021

The Honorable Jack Reed
Chairman
Committee on Armed Services
United States Senate
Washington, DC 20510

Dear Mr. Chairman:

The Department's response to section 750 of the National Defense Authorization Act for Fiscal Year 2020 (Public Law 116-92) is enclosed. Section 750 requires a study and report on traumatic brain injury (TBI) mitigation efforts.

This report summarizes the Department's findings that assessed 30 unique TBI treatments published in the past 5 years, and provides a roadmap addressing TBI mitigation efforts. Overall, an expanding inventory of evidence-based treatments exists that addresses short-term symptoms and chronic impairments resulting from TBI. However, research findings do not identify any specific treatment that directly helps repair of injured brain tissue.

Thank you for your continued strong support for our Service members. I am sending a similar letter to the Committee on Armed Services of the House of Representatives.

Sincerely,

A handwritten signature in black ink that reads "Virginia S. Penrod".

Virginia S. Penrod
Acting

Enclosure:
As stated

cc:
The Honorable James M. Inhofe
Ranking Member



PERSONNEL AND
READINESS

UNDER SECRETARY OF DEFENSE
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JUL 19 2021

The Honorable Adam Smith
Chairman
Committee on Armed Services
U.S. House of Representatives
Washington, DC 20515

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As stated

cc:
The Honorable Mike D. Rogers
Ranking Member

Report to Congress



Study and Report on Traumatic Brain Injury Mitigation Efforts Final Report

July 2021

In response to: Section 750 of the National Defense Authorization Act for Fiscal Year 2020 (Public Law 116-92)

The estimated cost of this report for the Department of Defense (DoD) is approximately \$87,000.00 for Fiscal Years 2020-2021. This includes \$82,000.00 in expenses and \$5,000.00 in DoD labor.

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INTRODUCTION

This report responds to section 750 of the National Defense Authorization Act (NDAA) for Fiscal Year (FY) 2020 (Public Law 116–92), which requires the Secretary of Defense to conduct a meta-analysis of evidence-based traumatic brain injury (TBI) mitigation efforts by the Secretary and related Federal agency partners, and efforts discussed in academic literature, that have demonstrated the best clinical effectiveness in the treatment of members of the Armed Forces for TBI. Additionally, section 750 requires the Secretary to develop and include in the study a roadmap for implementation across the Military Health System (MHS) of measures that address, with respect to the treatment of members for TBI, (1) the process for receiving such treatment; (2) patient outcomes; (3) cost; (4) patient and command satisfaction with such treatment; and (5) structured documentation to monitor system-wide implementation of the measures developed pursuant to (1)–(4) above. Lastly, section 750 requires the Secretary of Defense to submit a report on the results of this study to the Committees on Armed Services of the Senate and the House of Representatives.

BACKGROUND

The Department of Defense (DoD) defines TBI as a traumatically induced structural injury or physiological disruption of brain function as a result of an external force, which is indicated by new onset or worsening of at least one of the following clinical signs immediately following the event: any alteration in mental status, any period of loss (or decreased level) of consciousness, or any loss of memory for events immediately before or after the injury, (i.e., pre or post-traumatic amnesia). Since 2000, Service members have experienced 426,394 first lifetime TBIs; this reporting does not include Service members who incur subsequent TBIs. TBIs are classified as mild, moderate, severe, or penetrating, with the majority (greater than 80 percent) being mild.

TBI of any severity can cause symptoms across multiple functional domains, including physical, cognitive, and psychological. If TBI related impairments remain unaddressed, they can affect daily functioning, relationships, job performance, and quality of life. TBI mitigation efforts focus on managing the impact of these injuries on Service members and their families across the MHS.

LITERATURE REVIEW OF TRAUMATIC BRAIN INJURY MITIGATION EFFORTS

In alignment with the Department’s August 21, 2020 interim response to Congress, the DoD conducted a comprehensive literature review to meet the intent of the meta-analysis. A review of the literature on TBI treatment published between January 1, 2015 and May 31, 2020 entailed use of the PubMed® (National Center for Biotechnology Information, National Library of Medicine) and Google Scholar databases. A multidisciplinary team reviewed and evaluated articles for relevance and level of evidence. This review covered all severities of TBI (mild, moderate, and severe) and across all phases of recovery (acute, subacute, and chronic). Ultimately, 95 studies from this 5-year period met all criteria for inclusion. A small number of studies included patients with penetrating injuries. For the purpose of this review, the focus is on

severity, rather than cause of injury. It does not differentiate penetrating injuries, but they may be included under the severe category for some studies.

Review Results

The 95 studies included represent an assessment of 30 unique treatments, grouped into the following categories: **surgery (6), pharmacology (21), nutrition/supplements (7), rehabilitation (23), behavioral health (17), other (16), and multiple (5)**. Studies varied in size and methodologic quality. Fifty-three of the 95 articles reviewed reported positive treatment effects. The remaining 42 treatment studies found no benefit or mixed results from the treatment under investigation. One study of therapeutic hypothermia reported deleterious effects of treatment (i.e., increased incidence of pneumonia). Due to the breadth of therapies included, this review notes a wide variety of outcome measures, among which the most common were morbidity and mortality, functional/neurological recovery, behavioral health measures, post-concussive symptomatology, cognitive recovery, and quality of life (QOL).

Surgery. The acute phase of moderate and severe TBI may include surgical management, specifically craniotomy and/or craniectomy. The six studies in this category produced mixed results, finding reduced mortality among these patients without any improvement in morbidity and long-term outcomes, when compared with patients who only received medical management.¹⁻⁶ Overall, these decompressive craniectomy subjects who otherwise may have died, survived, but remain in a vegetative state.

Pharmacology. Nine unique treatments underwent evaluation in 21 studies. Currently, the most promising treatment is the antifibrinolytic drug tranexamic acid (TXA) in patients with acute intracranial bleeding. Three of five studies, including a very large multinational randomized-controlled trial,⁷ found a reduction in mortality and/or size of the hemorrhage when TXA was administered within 3 hours of injury.⁸⁻¹¹ Two clinical trials demonstrated that the glycoprotein cytokine erythropoietin reduces morbidity/mortality among subjects with acute TBI,^{12,13} however, a third trial showed no such benefit.¹⁴ The anticonvulsant gabapentin has been evaluated for the treatment of chronic post-traumatic headache; at least one study found that it provides short-term benefit for pain management.¹⁵ In this review, clinical trials of stimulants,¹⁶⁻²⁰ progesterone,²¹⁻²³ dopamine,²⁴ donepezil,²⁵ atorvastatin,²⁶ and glibenclamide²⁷ found no consistent benefit for the treatment of TBI.

Nutrition/Supplements. Small clinical trials investigated selenium,²⁸ vitamin D,²⁹ citicoline,³⁰ Cerebrolysin[®],³¹ antioxidants,³² an herbal supplement,³³ and probiotics.³⁴ These trials, of variable quality, do not provide sufficient evidence to support any recommendations regarding these treatments.

Rehabilitation. Rehabilitative treatments are common in the subacute and chronic phases of TBI recovery, and typically include physical and occupational therapy, speech language pathology, and/or neuropsychology. Twenty separate studies found that early multidisciplinary rehabilitation,³⁵⁻³⁸ cognitive rehabilitation,³⁹⁻⁴⁸ and physical activity/exercise⁴⁹⁻⁵⁴ generally enhance functional and cognitive recovery following a TBI event. Two additional studies of vestibular rehabilitation^{55,56} showed a trend towards benefit, as did a third study that examined community reintegration of veterans and self-reported outcomes.⁵⁷

Behavioral Health. Among 17 behavioral health intervention studies, cognitive behavioral therapy (CBT) was the most common⁵⁸⁻⁶³ and typically associated with improved post-concussive symptomatology. Individual studies also reported beneficial effects of CBT on behavioral health symptoms⁶⁰ and QOL/life satisfaction.⁶¹ Four studies of psychotherapeutic/educational interventions⁶⁴⁻⁶⁷ and four studies of social/emotional regulation⁶⁸⁻⁷¹ did not consistently find benefit from these interventions. Two studies of problem-solving therapies^{72,73} and one investigating eye movement desensitization and reprocessing⁷⁴ found some benefit from these interventions.

Other. Seven studies investigated hyperbaric oxygen therapy (HBOT), including several large prospective randomized clinical trials. These studies did not find HBOT to be effective in reducing post-concussive symptomatology.⁷⁵⁻⁸⁰ One meta-analysis of HBOT demonstrated short-term benefits for morbidity and mortality among individuals with moderate to severe TBI.⁸¹

Six studies investigated therapeutic moderate hypothermia, including a large systematic review. These studies did not find improvement in outcomes following this treatment.⁸²⁻⁸⁷ One trial suggested superiority of metabolic-targeted over body temperature-targeted hypothermia.⁸⁵ A separate trial reported a significant increase in pneumonia among the hypothermia group.⁸²

Three studies evaluated novel therapeutics such as repetitive transcranial magnetic stimulation (rTMS), biofeedback, acupuncture, creative arts therapy, mindfulness and animal engagement to include canine therapy, and showed potential in treating Service members with TBI. Currently many of these therapies are part of an interdisciplinary treatment model at the National Intrepid Centers in the MHS. However, most of the literature exploring these innovative therapeutics is preliminary with small sample sizes, lack of reported aggregated patient outcomes and mixed diagnoses participating in the intervention. A review of rTMS therapy found some evidence of improved post-concussive and behavioral health symptoms following treatment.⁸⁸ The Food and Drug Administration approved rTMS for treatment of several behavioral health conditions. Currently, rTMS is being used at some concussion clinics within the MHS.

Creative arts therapy is thought to improve communication between neuropathways and offer an opportunity for self-reflection and expression.⁸⁹ A systematic review showed improvements in cognitive, psychological and pain domains for patients participating in a creative arts program.⁹⁰ Animal assisted therapies such as canine or equine therapy or participation in service dog training has been studied in patient populations who are suffering from psychological trauma, which may be a co-occurring condition in the TBI population. Emerging evidence has shown greater improvements in psychological distress from participation in these therapies.⁹¹ Future directions in novel therapeutics include conducting randomized-controlled trials of effectiveness, investigation of long-term outcomes, and utilization of consistent outcome measures, increased study sample size, measures of patient satisfaction or qualitative patient experience and standardization of clinical practices.

Multiple. Two broad systematic reviews of treatments for post-concussive symptoms⁹²⁻⁹³ described beneficial effects of behavioral health interventions, including CBT and psychotherapy/education, and of cognitive rehabilitation. One of these also examined HBOT for

post-concussive symptoms and found either no or inconsistent benefit.⁹³ A third systematic review examined multiple treatments for moderate to severe TBI, and found an association between decompressive craniectomy and reduced mortality rate. However, this systematic review found no improvement in long-term outcomes; inconclusive results for pharmacologic and nutritional therapies; and potential deleterious effects of hypothermia and of steroids.⁹⁴ One study examined adherence to the Brain Trauma Foundation Guidelines for severe TBI with inconclusive results.⁹⁵ The final article in this category described a clinical trial that did not find benefit of therapeutic hypothermia in combination with progesterone.⁹⁶

Summary

This review provides a broad synopsis of TBI mitigation efforts published in the past 5 years and their general outcomes. The most promising treatment in the acute phase of care is TXA for reducing mortality and size of hemorrhage in moderate and severe TBI. In the subacute and chronic phases of TBI recovery, treatments primarily intend to manage symptoms and reduce long-term disability, rather than directly repair the injured brain. For this purpose, there were a variety of promising rehabilitative and behavioral health treatments, including early multidisciplinary rehabilitation, cognitive rehabilitation, and CBT.

ROADMAP

Development of a roadmap of TBI mitigation efforts entailed combining evidence gathered during the literature review process with information from a supplemental search and other available DoD resources. The supplemental search specifically targeted the five roadmap topics: (1) the process for receiving treatment; (2) patient outcomes; (3) cost; (4) patient and command satisfaction; and (5) structured documentation with respect to the treatment of Service members for TBI.

Process for Receiving Treatment

The DoD has implemented multiple initiatives to help ensure appropriate identification and treatment of TBI cases. The vast majority of injuries sustained by Service members are mild TBI, also known as concussion. All Service members exposed to a potentially concussive event (e.g., blow to the head, blast event, vehicle collision) in the deployed environment receive mandated screening per Department of Defense Instruction 6490.11, “DoD Policy Guidance for Management of Mild Traumatic Brain Injury/Concussion in the Deployed Setting,” updated on November 26, 2019. The TBI Center of Excellence (CoE) collaborates with multidisciplinary military and civilian experts to develop or revise standardized screening and evidence-based clinical recommendations to guide TBI treatment. Methods of knowledge translation into care include, but are not limited to, updates to DoD Clinical Practice Guidelines and Recommendations, training materials, and policy to reflect developments in the state of science.

The Quadruple Aim Performance Process (QPP) is one example of existing process initiatives to standardize care and ensure implementation of state-of-the-science care in the MHS. To accomplish these goals, the QPP measures whether a military medical treatment facility (MTF) provides Service members with concussion screening through the Military Acute Concussion

Evaluation 2 (MACE 2) instrument; conducts follow-up within 72 hours of concussion diagnosis; and applies the TBI CoE's Progressive Return to Activity Clinical Recommendation (PRA CR). The MACE 2 is a multi-modality assessment tool that assists medically trained personnel to screen for and identify mild TBI or red flags that indicate more severe injury. The PRA CR provides evidence-based guidance for the treatment of Service members after mild TBI to ensure optimal recovery and safe return to full duty. Individuals presenting with moderate or severe injury typically undergo treatment as inpatients in a hospital setting with comprehensive neurological management and/or intensive care. Facilities will discharge more severely injured patients to their homes with inpatient rehabilitation centers, long-term care facilities, or outpatient rehabilitation services, depending on their recovery trajectory. Service members retained on active duty who require specialty follow-up care can obtain referrals to multi-disciplinary concussion clinics, such as the National Intrepid Center of Excellence, an Intrepid Spirit Center, or identified MTFs.

Patient Outcomes

TBI outcomes vary substantially based on severity of injury, individual characteristics of the Service member, and other factors. For those with mild TBI, outcomes are generally favorable and mortality is very low. Most symptoms resolve within days to weeks.⁹⁷ Among the general population, approximately one in five individuals have symptoms that persist beyond 1 month and remain out of work at 6 months. Cases of protracted recovery are commonly associated with specific pre- or post-injury behavioral health symptoms.⁹⁸ Furthermore, some data suggest that Service members injured in combat have substantially higher rates of poor outcomes at 6–12 months post-injury, compared to civilians.⁹⁹ A deeper understanding of factors contributing to diminished outcomes among Service members could inform future TBI mitigation efforts. Another topic of interest is the potential impact of multiple concussions on patient outcomes. Ongoing efforts to address these topics include the congressionally mandated 15-Year Longitudinal Study on Traumatic Brain Injury Incurred by Members of the Armed Forces (section 721 of the John Warner NDAA for FY 2007 [Public Law 109–364]), and the DoD/Department of Veterans Affairs Long-Term Impact of Military-Relevant Brain Injury Consortium-Chronic Effects of Neurotrauma Consortium (LIMBIC-CENC) studies.

Outcomes of moderate to severe injury are significantly more variable and can often include substantial and disabling long-term neurological impairments. Compared to those with mild TBI, Service members with moderate to severe injury are significantly more likely to require hospitalization and inpatient rehabilitation, and are significantly less likely to remain on active duty.¹⁰⁰ On an individual patient basis, clinical outcomes measurement entails use of standard evaluation and assessments, most commonly through the Rancho Los Amigos Levels of Cognitive Functioning Scale, which determines the level of assistance an individual will likely need based on a graded level of responsiveness. Clinical assessment allows providers to plan or adjust treatment and prepare for patient discharge. TBI mitigation efforts reviewed for this report sought to evaluate outcomes ranging from survival to return to work. Continued research is required to identify advances in treatment that will further improve patient outcomes across the spectrum of severities.

Currently within the MHS, clinics are tracking and monitoring outcomes of patient care to adjust treatment plans and direct program changes. Enterprise solution requirements are currently

under review. The QPP metrics to collect acute concussion data will move the MHS closer to the ability to track TBI outcomes. Ongoing evaluation of metrics is critical to ensure the measures collected will track changes to outcomes as new treatments and technologies are translated into the clinical space.

Cost

To date, very limited information exists that examines cost related to specific TBI mitigation efforts and treatment decisions within the DoD. Current budgetary models account for overall costs and undergo review at the command and regional levels on a regular basis to determine need. A 2012 analysis of annual Veterans Health Administration expenditures found a four-fold increase in costs of care for Operation ENDURING FREEDOM and Operation IRAQI FREEDOM veterans with a diagnosed TBI, compared to those without a TBI.¹⁰¹ The ongoing health economics study at LIMBIC-CENC focuses on DoD costs for different TBI phenotypes, which may contribute to a more nuanced understanding of TBI expenditures in future programmatic evaluations. The Department recommends that the direction of future studies should focus on evaluating cost and utilization of TBI mitigation efforts within the MHS.

Patient and Command Satisfaction

Measures of patient or command satisfaction with particular treatment modalities were not found in this study. The MHS measures patient satisfaction more broadly to determine the availability and type of services provided, familiarity with availability and facilities, health status, satisfaction with system and quality, and other matters as appropriate. Health care scientists from the Defense Health Agency (DHA) Decision Support Division collect information to measure beneficiary and staff satisfaction and support key functions (e.g., improving quality of care/access). Results of surveys benchmarked against national norms undergo analyses and operationalization to drive system improvements. Specific to TBI, the Neuromusculoskeletal Community of Interest and the TBI Advisory Committee include representatives from each Military Service Branch. This allows for bidirectional communication between clinics and command to ensure command input and satisfaction with mitigation efforts.

The TBI CoE seeks to produce new knowledge in this area through support of 10 separate studies that examine access, use, costs, quality, delivery, organization, financing, and outcomes of health care services for Service members with TBI. The TBI CoE also supports five process improvement and quality improvement programs at five different MTFs to help to ensure provision of the highest level of care and responsiveness to patient needs.

Structured Documentation

Publications on TBI documentation are limited; however, substantial efforts are ongoing to develop and improve upon existing TBI documentation. Per the DHA Procedural Instruction 6025.06, "Standardized Templates for Primary Care Clinical Encounter Documentation," issued May 16, 2018, clinicians in MTFs will use standardized templates supporting clinical practice guidelines and care pathways for all outpatient visits. As part of the QPP initiative, clinicians treating Service members with concussion will document the use of MACE 2 and PRA CR during initial and follow-up encounters using the Tri-Service Workflow Form to the maximum

extent possible. In addition, the rollout of MHS GENESIS will make TBI-specific documentation available in the new electronic health record. Streamlined documentation will enable continuous improvement in future capabilities to evaluate and track patient outcomes.

CONCLUSION

Substantial research exists on TBI mitigation efforts published during the last 5 years. Overall, research findings do not identify any specific treatment that directly helps repair injured brain tissue. However, an expanding inventory exists of evidence-based treatments that address short-term symptoms and chronic impairments resulting from TBI. The MHS is committed to implementing and monitoring the most impactful TBI mitigation efforts available.

APPENDIX A: REFERENCES

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